



Association Between Serum Prolactin Level And Adverse Cardiovascular Events In Chronic Kidney Disease Patients

¹Dr. S. Sangeetha, ²Dr. B. Satish Kumar

¹Assistant Professor, ²Junior Resident,
Department Of General Medicine,

²Government Namakkal Medical College, Namakkal

¹Government Mohan Kumara Mangalam Medical College & Hospital Salem

***Corresponding Author:**

Dr. S. Sangeetha

Assistant Professor, Government Mohan Kumara Mangalam Medical College & Hospital Salem

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Abstract

Background : Chronic kidney disease is defined as a progressive loss in renal function over months or years leading to failure of excretory, metabolic, synthetic functions resulting in accumulation of nonprotein nitrogenous substances and present with a various number of clinical manifestations. Prolactin (PRL) is an anterior pituitary hormone. PRL clearance is reduced in CKD patients and its production is also to an extent altered. Increased level of serum prolactin is in turn associated with essential hypertension, an acute component of coronary syndrome, stroke ischemic variety, and also in preeclampsia. Elevated levels of serum prolactin which occurs in CKD can also contribute to vascular rearrangements. This might lead to cardiovascular outcomes among CKD patients.

Aim Of The Study: To study the correlation between serum prolactin level and adverse cardiovascular events in Chronic Kidney Disease (CKD) patients. To identify the association between elevated serum prolactin level and carotid intima-media thickness (CIMT) in CKD patients. To determine its prognostic outcome.

Materials And Methods: It was a prospective and analytical study of 50 patients admitted to our hospital with CKD and its complications. The study period was from Feb 2018 to Feb 2019 after informed consent patients were evaluated with laboratory investigations, clinical examination.

Result: In our study among 50 patients with CKD, 28 had raised serum PRL levels (about 56% of the study population) and among those 28 patients 17 had raised CIMT (about 60.71%). By statistical analysis, the T-test showed a strong correlation for hyperprolactinemia in CKD patients. The Chi-square test showed a significant association between hyperprolactinemia and raised CIMT among patients with CKD. By statistical analysis, we also found a correlation between raised PRL levels in CKD patients and T2DM, dyslipidemia, and occurrence of CAHD among them.

Conclusion: Serum prolactin levels are raised in patients with CKD. This hyperprolactinemia in CKD patients is associated with an increase in the CIMT and the occurrence of adverse cardiovascular events among them.

Keywords: CKD, Hyperprolactinemia, Carotid intima-media thickness, Cardiac dysfunction

Introduction

Chronic kidney disease refers to the irreversible loss of functions of the kidney which develops over years classically. At the initial stages, it manifests as a biochemical abnormality only and then occurs the

loss of excretory and endocrine, and metabolic functions of the kidney which leads to the manifestation of symptoms and signs of renal failure.[1] CKD is one of the chronic diseases prevailing in India with an approximate prevalence of

about 800 per million population (pmp) and the End-Stage Renal Disease (ESRD) is about 150-200 pmp. In India, a study from South India reported a Prevalence of impaired kidney function (eGFR<80 ml/min) to be 8.6 per 1000 after screening 25000 population.[2] Prolactin is a hormone that is secreted mainly by the anterior pituitary gland and also it is secreted by various tissues in the body. The main action of prolactin is to control breast development and lactation in women. In Male CKD patients, Hyperprolactinemia is associated with sexual dysfunction. Hyperprolactinemia is associated with loss of libido. Hyperprolactinemia is associated with impaired erection potency. High prolactin levels may be implicated for this abnormality. This may contribute to gynecomastia and sexual dysfunction in male CKD patients. Hyperprolactinemia in female CKD patients leads to mainly galactorrhoea and gonadal disturbances with irregularities of menstrual cycle commonly amenorrhoea. [3]CKD is characterized by elevation of serum prolactin level and also clearance of prolactin is reduced in CKD and its production is also altered and the biological activity is also increased. studies conducted recently show that prolactin has several biological actions that participate in the atherosclerotic process and endothelial dysfunction. The Carotid Intima-Media Thickness (CIMT) is the early marker for atherosclerosis. [4] Increased serum prolactin level is also associated with essential hypertension, ischemic stroke, coronary syndrome acute phase, and also in preeclampsia. The prevalence of hyperprolactinemia

in CKD varies from 30% to 65% [5]. Elevated serum prolactin level which occurs in cases of CKD may contribute to the vascular rearrangements in those cases. This might lead to any number of adverse cardiovascular outcomes among CKD patients. [6]

Materials And Methodology

The study was conducted on 50 patients with chronic kidney disease. All the patients were on the Conservative line of management. The study was conducted on patients admitted in Govt. Mohan Kumaramangalam Medical College Hospital, Salem between Feb 2018 to Feb 2019. The patients who fulfill the criteria for being diagnosed with CKD and who were on the Conservative line of treatment were taken into this study. The patients were evaluated with B-mode ultrasonography for CIMT measurement, ECG, and ECHO for the presence of Coronary Artery Heart Disease, and fasting serum prolactin level was measured in them to assess the presence of hyperprolactinemia. After selecting the appropriate patients, about 5 ml of blood is collected as a sample in non – heparinized bottle and sent for serum prolactin measurement and calculation. The Quantitative determination of Serum Prolactin level was done using a Fully Automated Bidirectionally Interfaced Chemi Luminescent Immunoassays. INCLUSION CRITERIA: Patients presented with established Chronic Kidney Disease irrespective of the etiology. Symptoms of uremia for 3 months or more than that. Elevated levels of blood urea, serum creatinine, and decrease in creatinine clearance.

Results And Observations

Table :1 Age Distribution

.Particulars	No. of respondents (n=50)	Percentage (100%)
35 to 40 yrs	7	14
41 to 50 yrs	13	26
51 to 60 yrs	20	40
61 to 65 yrs	10	20

Table :1 The patients with chronic kidney disease, in my study, were between 35 years to 65 years. Among 50 patients with chronic kidney disease, 7 patients were between 35 - 40 years of age, 13 patients were in the age group of 41-50 years, 20 patients were in the age group of 51-60 years, 10 patients were 61 years and above. Among 50 patients 34 patients were male patients and 16 patients were female patients

Table:2 Observation regarding Chronic Kidney Disease in this study

Creatinine clearance ml/min	CKD Stage	No. of Respondents	Percentage
30-60	III	1	2
15-30	IV	19	38
<15	V	30	60

Table :2 The duration of Chronic Kidney Disease in this study varied from 2 to 8 years. The creatinine clearance varied from 1.32-32.96. Among the 50 CKD patients 30 had creatinine clearance <15 ml/min, 19 patients had creatinine clearance 15-30 ml/min, 1 patient had creatinine clearance in the range of 30-60ml/min

Table :3 Blood Urea Level Distribution

Blood Urea[mg/dl]	No.of.Patients	Percentage
60-80	12	24
80-100	12	24
100-120	11	22
120-140	4	8
>140	11	22

Table :3 Among the 50 patients with CKD Blood urea values varied from 60 mg/dl to 199 mg/dl.

Table:4 Serum Creatinine Values

Sr. Creatinine level	No. of.Patients	Percentage
<5	23	46
5-10	18	36
10-15	7	14
15-20	2	4

Table :4 Among the CKD patients, serum creatinine values varied between 2.0 mg/dl to 16.2 mg/dl

Table:5 Ecg Evidence For Presence Of Chad

Particulars	No. of respondents (n=50)	Percentage (100%)
Absent	31	62.0

Present	19	38.0
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Table :5 Among the 50 patients who were part of this study, 18 patients were found to have evidence of coronary artery heart disease in ECG.

Table :6 Serum Prolactin

Particulars	No. of respondents	Percentage
	(n=50)	(100%)
Positive	28	56.0
Negative	22	44.0

Table :6 Serum prolactin level was measured for the 50 patients with chronic kidney disease using fully Automated Bidirectionally Interfaced Chemi luminescent Immuno Assay [C.L.I.A]. Among the 50 CKD patients, 28 patients had raised serum prolactin levels.

Table:7 CIMT

Particulars	No. of respondents	Percentage
	(n=50)	(100%)
Positive	18	36.0
Negative	32	64.0

Table :7 CIMT was measured for the 50 patients with chronic kidney disease using B mode ultrasonography. Among the 50 CKD patients, 18 patients had increased CIMT.

Discussion

The kidneys play a very important role in regulating the endocrine system in the body. The kidneys themselves produce a certain number of hormones. Hormones like erythropoietin and calcitriol are some examples. Kidneys also play an important role to a certain extent in the metabolism of some hormones. Kidneys also play an important role in the degradation of certain hormones like for example insulin and cortisol. [7]In chronic kidney disease patients, various endocrine systems in the body, various abnormalities are noted. There are alterations in mechanisms of signal feedback of various hormones in the human body. One of the major abnormalities of the endocrine system detected in patients with chronic kidney disease is an increase in

serum prolactin levels. Several studies regarding this have shown that serum prolactin levels remain elevated in patients with chronic kidney disease. This increase in the serum PRL occurs in both male and female patients with chronic kidney disease and the prevalence is about 30 % to 65%. Due to the reduced clearance by the kidneys, this occurs. There is an alteration in the dopaminergic activity in patients with chronic kidney disease. There is increased production of the prolactin hormone. This also takes part in the increased prolactin levels which are seen in this group of CKD patients. [8] In our study, we studied 50 patients who presented with chronic kidney disease. In our study, all patients were on a conservative line of management. Many studies have been conducted so far to establish the correlation regarding the levels of serum prolactin levels in CKD

patients and many studies were conducted to find out the involvement of the cardiovascular system in CKD cases.[9] Caticha et.al conducted serum prolactin estimation in a total of twelve patients with chronic kidney disease who were on a conservative line of treatment and thirty patients of chronic kidney disease who were on a hemodialysis basis and nineteen patients of chronic kidney disease who were post-transplant recipients with a functioning kidney. At the end of their study authors have shown that base point levels of serum prolactin remain elevated in patients with chronic kidney disease. This increase in the serum levels of hormone PRL was demonstrated in both CKD patients who were on a conservative line of treatment and in CKD patients who were on a hemodialysis routine. In their study, these authors also demonstrated that the elevated serum PRL hormone level showed a delay in response to stimulation produced by the TRH. [10] In this study, Raaz D et al also have shown that Serum prolactin levels remain normal in those CKD patients who have received a successful transplant with functioning kidneys. In this study, authors have established that the increase in the serum prolactin hormone levels is due to the decrease in renal catabolism and impaired regulation of the hypothalamic-pituitary axis. [11] As with other studies in our study also serum prolactin level was found to be elevated in 56 % of CKD patients. The remaining 44 % had normal serum prolactin levels. A similar study of evaluating things about hyperprolactinemia and impaired response by the pituitary to the suppression and the stimulation in the patients with chronic kidney disease was conducted by "Wallaschofski et.al Here the authors analyzed the reversibility of abnormalities those mentioned above with the management by the mode of Renal transplantation. In this study, authors have found out the increase in basal serum prolactin levels in patients with chronic kidney disease. In this study authors also have demonstrated that PRL hormone showed a lack of responsiveness to the suppressive as well as the stimulatory agents. They correlated this lack in responsiveness to pathology at the pituitary either the level of binding to the receptor or at the post-receptor level. Our study is consistent with the results of the above-mentioned studies in that in our study basal serum levels of hormone prolactin remained elevated in 56 % of CKD patients.[12] A statistically

significant association between increased serum PRL levels and the presence of chronic kidney disease. From several studies conducted recently, it has been shown that an increase in levels of serum prolactin is commonly found an abnormality in patients with Chronic Kidney Disease. However, there are only limited numbers of studies available regarding the implications of these increased serum prolactin levels in patients with chronic kidney disease. The only few studies conducted in the last decade on the consequence of this increased serum prolactin levels in patients with chronic kidney disease were mainly focused on reproductive and sexual dysfunction. Findings from several studies conducted in the non – renal population show Prolactin may have several other actions other than those what has already been well described. [13] From these studies, it has been shown that Prolactin is having actions on several other systems as well which accelerate the process of atherosclerosis. Increased serum levels of the hormone PRL seem to be observed in patients who present with essential hypertension and risk. [14] Dopaminergic control of prolactin and blood pressure' altered in those with essential hypertension. In their study authors studied the influence of dopamine on the levels of plasma catecholamine and plasma prolactin levels. The authors studied the mean arterial pressure (MAP) response to posture in an upright manner.[15] In this study authors also observed mean prolactin levels in patients with essential hypertension to be significantly higher over 24 hours of recumbent position. In their study authors also observed that treatment with bromocriptine had a lowering effect on mean arterial pressure levels throughout 24hrs in this hypertensive people group. Bromocriptine also eliminated the circadian rhythm of Prolactin secretion.[16] Thus at the end of their study authors conclude that circadian variations in the secretion of PRL and blood pressure appear to be influenced by a central and/or using the peripheral dopaminergic mechanism.[17] A decrease in the dopaminergic activity in essential hypertension may account, in part, for the disturbing factors in prolactin secretion and systemic hypertension. From several studies, it has been shown that serum prolactin levels increase in patients presenting with coronary syndromes during the acute phase. In addition increase in the serum level of PRL has also been

demonstrated in patients presenting with ischemic stroke. [18]The authors also positively established an independent association between serum PRL concentration and cardiovascular mortality increase in the level of serum PRL has been shown to do a causative role in HT complications of patients presenting with preeclampsia. In addition to this, it has been shown that an increase in the serum PRL levels plays a role in the development of heart failure that accompanies peripartum cardiomyopathy and also posts Partum cardiomyopathy as a cause. In one another study increased serum PRL levels predicted adverse cardiovascular events in patients specifically males with erectile dysfunction.[19] Using immunohistochemical analysis and with help of immunoelectron microscopy authors found out the abundant presence of prolactin receptors in the macrophages present by the lipid core which is the part of atherosclerotic plaques. Prolactin receptors were also numerously detected in the macrophages near the shoulder region of the plaques of atherosclerosis[20]. Over the end of their study authors concluded that PRL receptors are expressed in macrophages of the plaques (atherosclerotic) at the sites where most prominent inflammation occurs to an extent. In this study patients with creatinine level higher than 1.4 mg/dl was eligible for the study. Acute renal failure patients were excluded. In this study, CCA IMT was measured by B mode USG in high resolution both in longitudinal planes and transverse planes. This study was primarily done in patients with very less renal impairment and implied that risk factors (traditional) are important during renal impairment in the initial early stages. In our study, we have done an estimation of serum PRL levels in 50 chronic kidney disease patients. Among the 50 CKD patients, 28 had elevated serum prolactin levels which were about 56%. Increased serum prolactin levels had a statistically significant association with the presence of chronic kidney disease. [21]We further analyzed the presence of coronary artery heart disease and the association between PRL and diabetes and also with dyslipidemia in patients with increased serum PRL levels. We did ECG and ECHO analysis of patients who show an increased serum prolactin level. In our study among the 28 CKD patients with hyperprolactinemia 18 patients had coronary Artery Heart Disease, 14 patients had raised PRL and

T2DM, 17 patients had raised PRL and altered lipid profile which states about 64.28%, 50%, 60.71%. This showed a statistically significant association to exist between hyperprolactinemia in CKD patients with diabetes and dyslipidemia and the occurrence of CAHD among them.[22]

Conclusion

CKD is associated with raised serum levels of hormone PRL [Hyperprolactinemia]. Hyperprolactinemia is detected in 56 % (n=28) of our study group of patients with chronic kidney disease (n=50). Among the CKD patients with hyperprolactinemia, about 60.7% had evidence of increased CIMT when evaluated using high-resolution B mode Ultrasonography. From our study, we could conclude that hyperprolactinemia in patients with chronic kidney disease may be a risk factor for the increase in CIMT and future risk of adverse cardiovascular events among them.

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